FORM PTO-1390 (REV 10-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C.371

ATTORNEY'S DOCKET NUMBER: **MIJ-001US**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/297652

INTERNATIONAL APPLICATION	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU97/00747	**04 November 1997 (04.11.97)**	**04 November 1996 (04.11.96)**

TITLE OF INVENTION

SYNERGISTIC GOLD-CONTAINING COMPOSITIONS

APPLICANT(S) FOR DO/EO/US

Richard Edward THOMAS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C.371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371 (b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. **(3 sheets);**
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). **(28 sheets and 2 sheets of drawings);**
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(unexecuted) (3 sheets);**
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **(2 sheets) with Form PTO-1449 (1 sheet);**
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
13. ☒ A FIRST preliminary amendment. **(6 sheets);**
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: **Transmittal Letter (2 sheets in duplicate); PCT Request (3 sheets); PCT Notification of Receipt of Record Copy (PCT/IB/301) (1 sheet); PCT Notification Concerning Submission of Priority Documents (PCT/IB/304) (1 sheet); PCT Notice Informing the Applicant of the Communication of the International Application into the Designated Offices (PCT/IB/308) (1 sheet); PCT Information Concerning Elected Offices Notified of their Election (PCT/IB/332) (1 sheet); PCT Notification of the Recording of a Change (PCT/IB/306) (1 sheet); PCT International Published Application (WO 98/19683) (with International Search Report attached) (33 sheets); PCT Notification of Transmittal of the International Search Report of the Declaration (7 sheets); PCT Demand (3 sheets); PCT Notification of Receipt of Demand (1 sheet); PCT First Written Opinion (dated 22 June 1998) (4 sheets); Response to First Written Opinion (11 sheets); PCT Second Written Opinion (dated 23 October 1998) (5 sheets); PCT International Preliminary Examination Report (13 sheets); Certificate of Express Mailing (1 sheet); Check in the amount of $638 (representing filing fee based on small entity status); and Return Postcard.**

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NO.
	PCT/AU97/00747	**MIJ-001US**

17. ☒ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) .(a/o November 1, 1998):

Search Report has been prepared by the EPO or JPO.....**$840**

International preliminary examination fee paid to USPTO (37 CFR 1.482).....**$670**

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....**$760**

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$970**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$96**

ENTER APPROPRIATE BASIC FEE AMOUNT =				**$970**	
Surcharge of **$130.00** for furnishing the oath or declaration later than 20 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$---	
CLAIMS	**NUMBER FILED**	**NUMBER EXTRA**	**RATE**		
Total claims	**37** -20 =	**17**	X **$18.00**	**$306**	
Independent claims	**2** -3 =	**0**	X **$78.00**	$---	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **260.00**	$---	
TOTAL OF ABOVE CALCULATIONS =				**$1276**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(Enclosed)**				**$638**	
SUBTOTAL =				**$638**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$---	
TOTAL NATIONAL FEE =				**$638**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$---	
TOTAL FEES ENCLOSED =				**$638**	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$ 638** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **12-0080**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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38,872
REGISTRATION NUMBER

(Atty Docket No.: MIJ-001US)

IN THE UNITED STATES PATENT DESIGNATED OFFICE (DO/US)
(National Phase of International App.: PCT/AU97/00747)

In re the
application of: **Richard Edward THOMAS**

International Application No.: **PCT/AU97/00747**

International Filing Date: **04 November 1997**

Serial No.: **Not yet assigned**

Filed: **Herewith**

For: **SYNERGISTIC GOLD-CONTAINING COMPOSITIONS**

Attorney Docket No.: **MIJ-001US**

BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination of the above-referenced application, please amend the claims as follows:

In the claims:

Please amend claims 2 - 7, 10 - 14, 16 - 28, and 35 - 37 as follows (all of the pending claims, whether or not amended, are set forth below for clarity):

1. A method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

2. (Amended) A method of treating an immune-mediated disorder according to claim 1, wherein the disorder has an inflammatory component and a cellular hyperproliferation component.

3. (Amended) A method of treating an immune-mediated disorder according to [any one of the preceding claims] claim 1, wherein the gold compound and the at least one corticosteroid are administered simultaneously.

4. (Amended) A method of treating an immune-mediated disorder according to [any one of the preceding claims] claim 1, wherein the gold compound and the at least one corticosteroid are administered sequentially.

5. (Amended) A method of treating an immune-mediated disorder according to claim 4, wherein the at least one corticosteroid is administered after the gold compound.

6. (Amended) A method of treating an immune-mediated disorder according to [any one of the preceding claims] claim 1 comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

7. (Amended) A method according to [any of the preceding claims] claim 1, wherein the disorder is an immune-mediated dermatological disorder.

8. A method according to claim 7, wherein the disorder is psoriasis.

9. A method according to claim 7, wherein the disorder is dermatitis.

10. (Amended) A method according to [any one of claims 1 to 6] claim 1, wherein the disorder is rheumatoid arthritis.

11. (Amended) A method according to [any one of the preceding claims] claim 1, wherein the gold compound is lipid soluble.

12. (Amended) A method according to [any one of the preceding claims] claim 1, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards cellular hyperproliferation in preference to inflammation.

13. (Amended) A method according to claim 12, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and hydrocortisone.

14. (Amended) A method according to [any one of the preceding claims] claim 1, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards inflammation in preference to cellular hyperproliferation.

15. A method according to claim 14, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and mometasone furoate.

16. (Amended) A method according to claim 10_2 wherein the corticosteroid is selected from the group [comprising] consisting of hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-privalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

17. (Amended) A method according to claim 16, wherein the corticosteroid is selected from the group [comprising] consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

18. (Amended) A method according to [any one of the preceding claims] claim 1, wherein the gold compound is auranofin.

19. (Amended) A method according to [any one of the preceding claims] claim 1, wherein the gold compound is administered systemically.

20. (Amended) A method according to [any one of claims 1 to 18] claim1, wherein the gold compound is administered orally.

21. (Amended) A method according to [any one of claims 1 to 18] claim 1, wherein the gold compound is administered locally.

22. (Amended) A method according to [any one of claims 1 to 18] claim 1, wherein the gold compound is administered topically.

23. (Amended) A method according to [any one of claims 1 to 18] claim 1, wherein the gold compound is administered by intra-articular injection.

24. (Amended) A method according to [any one of the preceding claims] claim 1, wherein the at least one corticosteroid is administered systemically.

25. (Amended) A method according to [any one of claims 1 to 23] claim 1, wherein the at least one corticosteroid is administered orally.

26. (Amended) A method according to [any one of claims 1 to 23] claim 1, wherein the at least one corticosteroid is administered locally.

27. (Amended) A method according to [any one of claims 1 to 23] claim 1, wherein the at least one corticosteroid is administered topically.

28. (Amended) A method according to [any one of claims 1 to 23] claim 1, wherein the at least one corticosteroid is administered by intra-articular injection.

29. A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

30. A pharmaceutical composition according to claim 29, wherein the composition is formulated for systemic administration.

31. A pharmaceutical composition according to claim 29, wherein the composition is formulated for oral administration.

32. A pharmaceutical composition according to claim 29, wherein the composition is formulated for local administration.

33. A pharmaceutical composition according to claim 29, wherein the composition is formulated for topical administration.

34. A pharmaceutical composition according to claim 29, wherein the composition is formulated for administration by intra-articular injection.

35. (Amended) A pharmaceutical composition according to [any one of claims 29-34] claim 29, wherein the corticosteroid is selected from the group [comprising] consisting of hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-privalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

36. (Amended) A method according to claim 35 wherein the corticosteroid is selected from the group [comprising] consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. (Amended) A method according to [any one of claims 29-36] claim 29, wherein the gold compound is auranofin.

REMARKS

Claims 2 - 7, 10 - 14, 16 - 28, and 35 - 37 have been amended to replace multiple dependencies with single dependencies and to correct matters of form. No new matter has been added.

Respectfully submitted,

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Dated: May 4, 1999

Applicant or Patentee: Richard Edward THOMAS
Serial or Patent No.: U.S. National Phase of PCT/AU97/00747
Filed or Issued: 04 November 1997
Title: SYNERGISTIC GOLD-CONTAINING COMPOSITIONS

Attorney's Docket No.: MIJ-001US

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

☐ the owner of the small business concern identified below:

☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN Medical Innovations Limited
ADDRESS OF SMALL BUSINESS CONCERN Unit 2, 83-85 Whiting Street, Artarmon, NSW 2064, Australia

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

☐ the specification filed herewith with title as listed above.

☒ the application identified above.

☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME
ADDRESS
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME
ADDRESS
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Jeffrey GOLDER

TITLE OF PERSON OTHER THAN OWNER Director

ADDRESS OF PERSON SIGNING 24 Bassett St Mona Vale NSW 2103.

SIGNATURE Jeffrey Golder DATE 2/6/99

TITLE: SYNERGISTIC GOLD-CONTAINING COMPOSITIONS

TECHNICAL FIELD

The present invention relates to pharmaceutical compositions comprising a gold compound in combination with a corticosteroid and their use in the treatment of dermatological disorders.

BACKGROUND OF THE INVENTION

The effectiveness of gold compounds in the treatment of rheumatoid arthritis has been known since the 1960s. More recently, gold complexes have been employed as therapeutic agents in the treatment of rheumatoid arthritis but their exact mechanism is still unknown. The most commonly used complexes have been water soluble, parenterally administered gold (Au(I)) thiolates such as aurothiomalate (Myocrisin®) and aurothioglucose (Solganol®). Subsequently, a number of alkylphosphine gold complexes displayed anti-arthritic activity when administered orally to adjuvant arthritic rats. Auranofin (1-thio-β-D-glucopyranose 2,3,4,6-tetraacetato-S)-(triethylphosphine)-Au(I)) was among the most potent and efficacious of the compounds tested and is now used in the treatment of rheumatoid arthritis in man.

Gold compounds have also been administered by intravenous and oral routes for the treatment of asthma, tuberculosis, pemphigus vulgaris, various forms of arthritis, cancer and infection. However, treatment with gold compounds has been frequently associated with unacceptable and on occasions serious side effects.

Corticosteroids have also found similar therapeutic applications. The success of topical corticosteroids in the therapy of inflammatory and proliferative disorders of the skin has led to vigorous development of new corticosteroids since their first topical use. An increase in potency has been achieved by chemical modification of the natural corticosteroid, hydrocortisone, without precise knowledge of the mechanism of action of corticosteroids. The development of more potent corticosteroids has extended their usefulness in a wide variety of skin diseases, but, especially with long term use, has led to unwanted effects. Systemic effects such as hypothalmic pituitary-adrenal-axis depression were already known from the systemic use of corticosteroids. Local side effects after topical application were observed only with the more potent synthetic steroids.

The most common serious side effects of topical corticosteroids are thinning of the skin, striae and telangiectasia. During long term treatment with very potent

corticosteroids, inflammatory cells are affected and the proliferation of keratinocytes and the activity of fibroblasts are also inhibited.

Fibroblasts synthesize important structural and functional components of the dermis, namely collagen, elastin and glycosaminoglycans. The inhibition of keratinocyte proliferation leads to thinning of the epidermis. Although the effect on the epidermis is usually reversible, the dermis can be irreversibly damaged.

Recently, topical formulations of gold organic complexes have found use in the treatment of skin disorders such as psoriasis. Thus, Australian Patent No. 616,755, describes the use of a topical formulation of auranofin in combination with a corticosteroid in the treatment of local inflammatory conditions such as those associated with psoriasis. In particular, treatment with a formulation comprising auranofin and betamethasone dipropionate demonstrated a remarkable synergy of action when compared to same concentrations of individual active ingredients. The finding that a gold compound can synergise with a corticosteroid enabled the use of considerably lower levels of both the gold compound and a corticosteroid in the formulations, thus enabling more effective therapy while obviating the well known side effects associated with the use of either gold compounds or corticosteroids alone.

Dermatological disorders are frequently associated with manifestations other than just inflammation. For example, psoriasis also contains a component of cellular hyperproliferation (hyperplasia), the mechanism of which is fundamentally different from that of inflammation and thus may not necessarily be affected by the topical gold/corticosteroid formulations. Furthermore, the inflammatory component of different dermatological conditions may range from very mild to very severe, necessitating variations in the formulation, in particular the choice of corticosteroid which would enable not only effective and appropriate treatment of the inflammatory component, but also provide the differential action in dermatological conditions where there is an additional component such as cellular hyperproliferation.

Other immune, autoimmune and infection disorders can also be associated with multiple manifestations, where effective treatment may rely on targeting only one of the manifestations of the disorder, or more than one, depending on the disorder treated and the assessment of the patient.

The present invention is based on a surprising finding that important differences exist between corticosteroids with respect to the degree of potentiation of effects and the

type of effect potentiated, when combined with a gold compound. That is to say, different corticosteroids, when combined with a gold compound, do not all have the expected similarity of synergistic action against inflammation and also demonstrate differential synergistic action with respect to inflammation and hyperplasia. In the compositions of the present invention certain corticosteroids synergise with the gold compound to provide a greater effect on the inflammatory component of a disorder, such as psoriasis, while other corticosteroids give rise to compositions with preferential effects on cellular hyperproliferation. It is contemplated that the compositions of the present invention could be effectively used also for the treatment of a variety of systemic, tissue-specific or localised immune, autoimmune and inflammatory disorders.

SUMMARY OF THE INVENTION

According to a first aspect the invention consists in a method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

According to a preferred embodiment the present invention consists in a method of treating an immune mediated disorder according to the first aspect comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

According to another preferred embodiment the present invention consists in a method of treating an immune-mediated disorder having multiple components, comprising the step of administering to a patient requiring such treatment one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to provide a composition with equal synergistic action towards each component of said disorder.

According to another preferred embodiment the present invention consists in a method of treating an immune-mediated disorder having one or more components,

comprising the step of administering to a patient requiring such treatment a composition comprising a gold compound and one or more compositions comprising one or more corticosteroids wherein the corticosteroid is selected to provide a composition with preferential synergistic activity towards one of the components of said disorder and wherein the composition comprising a gold compound is administered orally and the one or more compositions comprising one or more corticosteroids is administered topically, in amounts effective to provide a composition of gold and a corticosteroid having preferential synergistic action towards said component.

Preferably the component of the immune-mediated disorder is an inflammatory component and/or a cellular hyperproliferation component and the composition comprises at least two corticosteroids, one of which is selected to provide a composition with preferential synergistic action towards the inflammatory component and the second corticosteroid is selected to provide a composition with preferential synergistic action towards the cellular hyperproliferation component of said disorder.

Preferably the disorder to be treated is an immune-mediated dermatological disorder which is associated with more than one component. Examples of immune-mediated dermatological disorders include psoriasis or dermatitis such as contact, atopic or seborrheic dermatitis. Other disorders include rheumatoid arthritis. Typical components of such disorders include an inflammatory component and/or a cellular hyperproliferation component. The corticosteroid can be selected to provide a composition with synergistic activity towards cellular hyperproliferation in preference to inflammation or *vice versa*. Such a corticosteroid can be, for example, betamethasone dipropionate, fluocinolone acetonide or hydrocortisone. In cases where inflammation needs to be targeted in preference to cellular hyperproliferation, the corticosteroid can be betamethasone dipropionate, fluocinolone acetonide or mometasone furoate.

The composition is suitably formulated for topical administration.

Where the immune-mediated disorder is characterised by a number of different components, the preferred method of treatment could employ one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroids are selected to provide composition(s) with preferential activity towards only one of the components of said disorder. Thus the treatment of each individual

component is achieved through use of composition(s) comprising one or more selected corticosteroids, which may be applied in the form of two or more separate compositions or a single composition comprising two or more corticosteroids.

Preferably the gold compounds used in the present invention are lipid soluble. Even more preferably the gold compounds used are formulated for topical application. However, it will be understood that systemically or locally administered compositions are also within the scope of the present invention including those administered by injection, preferably intra-articularly. In this regard the corticosteroid can be formulated for oral, topical, systemic or local administration.

According to second aspect the present invention consists in a pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

Preferably the gold compound is auranofin and the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate or fluocinolone acetonide. More preferably the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide.

BRIEF DESCRIPTION OF FIGURES

Figure 1: A histogram showing the effects of auranofin and glucocorticoids alone or in combination on TPA-induced epidermal hyperplasia. BMD: betamethasone dipropionate; HYD: hydrocortisone; FA: fluocinolone acetonide, MMF: mometasone furoate; AF: auranofin. Bars indicate standard error of the mean (SEM).

Figure 2: A histogram showing the effects of auranofin and glucocorticoids alone or in combination on TPA-induced inflammatory cell infiltration. BMD: betamethasone dipropionate; HYD: hydrocortisone; FA: fluocinolone acetonide; MMF: mometasone furoate; AF: auranofin. Bars indicate standard error of the mean (SEM).

DESCRIPTION OF THE PREFERRED EMBODIMENT

For convenience, a TPA (12-*O*-tetradecanoylphorbol 13-acetate), model of psoriasis, as an example of an immune-mediated disorder which has an inflammatory as well as a cellular hyperproliferation component, will be used to demonstrate differential action of different corticosteroids as well as differential action of different formulations of a gold compound and a corticosteroid.

Although psoriasis does not occur in animals other than humans, studies have shown that the application of TPA produces an inflammatory reaction with epidermal thickening that resembles psoriasis in many ways. It produces epidermal hyperplasia and inflammatory cell infiltration into the dermis, both of these features are also characteristic of psoriasis.

TPA increases the activity of the phospholipase C/inositol trisphosphate/ diacylglycerol system. This system activates the protein kinase C and arachidonic acid pathways. Both these systems have been implicated in the pathogenesis of psoriasis. TPA-treated mouse is believed to be a suitable model for psoriasis. This animal model will be used to show differential actions of different corticosteroids and the synergistic effects of compositions comprising a gold compound and a corticosteroid.

Three parameters have been measured: skin-fold thickness, epidermal hyperplasia and inflammatory cell infiltration into the dermis. These features, particularly the last two, are the hallmarks of psoriasis. It is noteworthy however, that the current findings clearly have implications beyond mere treatment of dermatological disorders. Systemic or tissue inflammatory and hyperplastic conditions could also benefit from treatment with the compositions of the present invention.

Topical Corticosteroids

Topical corticosteroids can be grouped according to their strength: weak, medium, strong and very strong. Vasoconstriction assay is considered the best method of assessing the potency of various preparations. It is not known whether the measurement of vasoconstriction predicts anti-inflammatory activity. Other methods of assaying that are available include clinical trial, dermal thickness radiograph, biopsy for assessing epidermal thinning, and mitotic inhibition assays.

A useful clinical guide to the relative potencies of topical corticosteroid preparations is shown in Table 1, the rank order arrangement being approximately the same for ointments and creams. The preparations in each group are only roughly equipotent.

Table 1 A guide to the clinical potencies of topical corticosteroids

Weak	Medium	Strong	Very Strong
Dexamethasone 0.01%	Alclometasone dipropionate 0.05%	Amcinonide 0.1%	Beclomethasone dipropionate 0.5%
Fluocinolone acetonide 0.0025%	Betamethasone valerate 0.025%	Beclomethasone dipropionate 0.025%	Clobetasol propionate 0.05%
Hydrocortisone 0.5% and 0.1%	Clobetasone butyrate 0.05%	Betamethasone benzoate 0.025%	Diflucortolone valerate 0.3%
Hydrocortisone acetate 1%	Dexamethasone 0.05%	Betamethasone dipropionate 0.05%	Fluocinolone acetonide 0.2%
Methylprednisolone acetate 0.25%	Flumethasone pivalate 0.02%	Betamethasone valerate 0.1%	
	Fluocinolone acetonide 0.01%	Budesonide 0.025%	
	Fluocortin butylester 0.75%	Desonide 0.05%	
	Fluocortolone 0.2%	Dexamethasone 0.25%	
	Flurandrenolone 0.0125%-0.025%	Diflorasone diacetate 0.05%	
	Hydrocortisone 1% with urea	Diflucortolone valerate 0.1%	
		Fluclorolone acetonide 0.025%	
		Fluocinolone acetonide 0.025%	
		Fluocinonide 0.05%	
		Fluocortolone 0.5%	
		Fluprednidene acetate 0.1%	
		Flurandrenolone 0.05%	
		Halcinonide 0.1%	
		Hydrocortisone butyrate 0.1%	
		Mometasone furoate 0.1%	
		Triamcinolone acetonide 0.1%	

The invention will now be more particularly described with reference to specific embodiments by way of non-limiting example only.

Example 1: Animal treatment and methods of measurement

Materials

Auranofin was kindly donated by Smith Kline and Beecham Pharmaceuticals, King of Prussia, Philadelphia, USA.

Alclometasone dipropionate, betamethasone dipropionate, betamethasone valerate, betamethasone (as free alcohol) and mometasone furoate were kindly donated by Schering-Plough Pty. Ltd., Baulkham Hills, NSW, Australia.

Halcinonide, Hydrocortisone and Triamcinolone acetonide were kindly donated by Bristol-Myers Squibb Pharmaceuticals Pty. Ltd.

Dexamethasone was kindly donated by Roussel Uclaf, Paris, France.

Fluocortolone 21-pivalate was kindly donated by Schering AG, Berlin, Germany.

12-*O*-Tetradecanoylphorbol 13-acetate, fluocinolone acetonide, aluminium potassium sulphate, sodium hydrogen carbonate, sodium iodate, magnesium sulphate, eosin Y, phloxine, calcium carbonate, formaldehyde acetic acid (17 M), thymol, xylene, haematoxylin and "Paraplast" tissue embedding medium were obtained from Sigma Chemical Company, Castle Hill, NSW, Australia.

Sorbolene cream A.P.F. was obtained from Wille Laboratories, Carole Park, Queensland, Australia.

Preparation of auranofin 0.2 % solution

Auranofin (20 mg) was dissolved in 10 mL of acetone to give the strength 0.2%. Auranofin solution was freshly prepared for each experiment.

Preparation of auranofin ointment

Various strengths of auranofin ointment were made according to the formula as shown below:

strength (% w/w)	auranofin	propylene glycol (10%)	white soft paraffin
0.20	40 mg	2 g	to 20 g
0.50	100 mg	2 g	to 20 g

Methods of animal treatment

Female BALB/c mice aged 6 to 8 weeks were obtained from the University of Sydney, and treated according to a protocol approved by the University of Sydney Animal Care and Ethics Committee.

The mice were housed in stainless steel cages, 6 mice per cage under normal laboratory conditions (room temperature at about 22°C) at least 7 days before the experiments for acclimatization. Food and water were allowed *ad libitum* throughout the experiment period. The backs of the mice were shaved with an electric clipper two days before each treatment and only those mice showing no hair regrowth were used (i.e., the mice in the resting phase of the hair growth cycle were selected). During treatment, the mice were held with their tails and put on top of the cage so that they grasped the cage and rested there. The solutions were applied to an area approximately 2 cm x 2 cm on the shaved back of the mice by using a "Pipetman" to apply the solution. If auranofin ointment or ointment base was applied, the amount was standardized by using a microspatula which was crimped at one end, the ointment was then put into the ridge and the excess removed by means of another microspatula and applied sparingly twice a day. After a fixed time, the mice were killed routinely by cervical dislocation between 9 a.m. and 11 a.m. to avoid variations due to circadian rhythms, and an area (1 cm x 1 cm) was excised from the centre of the treated area by scalpel and scissors. The rest of the tissues were disposed by combustion. The tissues were then fixed, embedded, sectioned and stained.

Methods of preparation of skin sections

The method of preparation of skin sections was adapted from a method developed by the Department of pathology, University of Sydney and shown to be successful.

Fixation, embedding, sectioning and staining

Standard preparation procedures were used. Briefly, the tissue was fixed in 10% buffered formalin for 24 hours, washed in tap water for 10 minutes and then processed in an automatic tissue processor (Tissue-Tek VIP 200). In the automatic tissue processor, the tissue was dehydrated in a graded series of alcohol and xylene at room temperature, and was then infiltrated with 4 changes of paraffin wax ("Paraplast" tissue mounting medium) at 60°C. It was finally embedded in fresh paraffin wax.

Sections 5 μm thick were cut on an American Optical Spencer "820" microtome. The sections were then mounted on clean microscope slides using wood glue ("Selleys" Aquadhere, 1:100 dilution with water) as adhesive, and were allowed to dry in an oven at 45°C for at least 2 hours (usually overnight).

After the sections were blued in the Scott's blueing solution, they were examined under microscope to assess that nuclei were clearly stained and cytoplasm was unstained.

Measurement of skin-fold thickness

The back skin of shaved mice was folded and measured by using a "Etalon" micrometer screw gauge. One measurement was taken for each mouse.

Measurement of epidermal thickness

Epidermal thickness was determined by image analysis. This image analysis system was a minicomputer (Tracor Northern TN8500) attached to a light microscope (Zeiss Axioplan) and a camcorder (Sony DXC-3000P). Sections were taken from each tissue block and 20 measurements were taken at fixed intervals from each section. The average value for the 20 measurements was obtained and entered as one value for each mouse. The mean and SEM for the six mice in each treatment group were calculated.

Measurement of infiltration of inflammatory cells

Infiltration of inflammatory cells was determined by the same image analysis system using the section taken from the block of mouse skin embedded in paraffin wax or Spurr's resin and stained with haematoxylin and eosin or toluidine blue respectively. For each section, 10 fields, unless otherwise stated, were chosen randomly and the cell density per mm^2 of field determined. The average value for the 10 fields was obtained and entered as one value for each mouse. The mean and SEM for the six mice in each treatment group were calculated.

The measurement of the inflammatory cell infiltration included the background values which included other materials in the dermis stained in the same way. However, the increase, if there is any, reflects the migration of inflammatory cells.

Data treatment

The per cent inhibition of drug on TPA-induced skin responses (i.e., epidermal hyperplasia, inflammatory cell infiltration and skin-fold thickness) was calculated by using the following formula:

$$\text{Per cent inhibition} = \frac{\text{Total response due to TPA} - \text{Total response due to drug}}{\text{Total response due to TPA} - \text{Total response due to acetone}} \times 100\%$$

It is commonly found that the relationship between dose (or concentration) and response may be satisfactorily described using the Michaelis Menton equation or a variant of it such as the Hill equation. This provides estimates of (a) the potency, (b) the efficacy or maximum effect (E_{max}) and the slope of the log concentration-response curve by using Hill coefficient (γ). The Hill Equation may be expressed as follows:

$$E = \frac{Emax \times C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}}$$

where IC_{50} is the drug concentration producing 50% of the maximal response and E_{max} refers to the maximal effect produced by the drug and is also termed efficacy. Efficacy is the measurement of the intrinsic ability of a drug to initiate a response once it occupies receptor sites. Measurement of both the E_{max} and the IC_{50} (potency) are clearly crucial when comparing the activity of similar drugs. The Hill coefficient (γ) measures the slope of the dose-effect curve which can be markedly influenced by the shape of the curve that describes the binding of the drug to the receptor. For many drugs, γ lies between 0.6 and 1.5. The use of the Hill coefficient not only improves the fit of the data, but also indicates the influence of changes in dose or concentration on response: for example, when γ is greater than 1, the slope is very steep, meaning that a marked change in drug effect is associated with a small change in dose or concentration of drug. On the other hand, when γ is less than 1, with a shallow hyperbolic concentration effect relationship, the activity occurs over a wide range of drug levels. Hence, the different values of γ can dramatically affect the drug's clinical usefulness

In the present study, concentration-response curves were obtained for a series of corticosteroids. In these experiments, curve fitting was accomplished using a computer programme called "The Scientist" (MicroMath Scientific Software, Salt Lake City, Utah, USA.) in which the parameters, E_{max}, IC_{50} and Hill coefficient (γ) for each steroids were estimated by using non-linear regression and least square fits.

The overall significance of differences between treatments was determined by one way analysis of variance, while the Tukey HSD test was used to examine the significance level of specific contrasts. The Systat for Windows program (Systat Inc, Evanston, Illinois, USA.) was used.

Example 2: Effects of TPA on skin of mice

This study was conducted to determine the time course of effects produced by applying TPA to mice and killing at intervals of 1, 2, 3, 5 and 8 days. Peak times for

epidermal hyperplasia, dermal inflammation and skin-fold thickness were determined. The object of this study was to determine the best time to sacrifice TPA-treated mice so as to obtain the maximum response to TPA. The literature indicates that TPA-induced epidermal hyperplasia and dermal inflammation peak at different times. It was thus expected that a compromise time would have to be selected.

Forty two female BALB/c strain mice were divided into the treatment groups and the mice were treated with a single application (100 μL) of TPA (0.01% in acetone) and sacrificed at days 1, 2, 3, 5 and 8 and the time course of TPA effects on epidermal hyperplasia, dermal inflammatory cell infiltration and skin-fold thickness measured as described in Example 1.

The skin responses to TPA are summarized below:

	Day 1	Day 2	Day 3	Day 5	Day 8
Increase in epidermal thickness	326%	382%	393%	270%	130%
Increase in dermal inflammatory cell density	397%	296%	272%	280%	225%
Increase in skin-fold thickness	193%	142%	124%	116%	107%

The experiment showed that a single application of TPA caused epidermal thickening, dermal inflammation and an increase in skin-fold thickness that lasted for at least 8 days. The peak effects were observed at 72 hours for epidermal hyperplasia and at 24 hours for dermal inflammation and skin-fold thickening.

Based on these results it was decided that an appropriate compromise, for most experiments, would be to sacrifice the animals 24 hours after a single application of TPA. This would result in maximum effects for inflammation and skin-fold thickness and near maximum effects for epidermal hyperplasia (over 80% of peak effect). Unless otherwise stated, mice were sacrificed 24 hours after the application of TPA.

Example 3: Action of Different Corticosteroids

In the first instance the ability of corticosteroids alone to inhibit TPA lesions was investigated. The following groups of corticosteroids were tested (the classification of the potencies of corticosteroids is dependent on the concentration used, the composition of the vehicle and the effect being studied) (Table 1).

Low potency: betamethasone, dexamethasone, hydrocortisone, hydrocortisone acetate.

Medium potency: alclometasone dipropionate, fluocortolone 21-pivalate.

High potency: betamethasone dipropionate, betamethasone valerate, fluocinolone acetonide, halcinonide, mometasone furoate, triamcinolone acetonide

Mice were divided into treatment groups. TPA and corticosteroids were premixed to the concentrations required and applied to the backs of mice immediately. For those steroids not very soluble in acetone (i.e., betamethasone, dexamethasone, hydrocortisone and hydrocortisone acetate), the drugs were dissolved in 100 μL dimethylformamide before further dilution with acetone. The efficacy of corticosteroids in inhibiting epidermal hyperplasia, inflammatory cell infiltration and skin-fold thickness was assessed as described previously. Concentration-response curves were determined after computer-fitting of data. The curve fitting technique was generated by a computer programme called "The Scientist" in which the parameters in the Hill Equation were generated. These included E_{max}, IC_{50}, and the Hill coefficient (γ) for each steroid. Concentration-response curves for each steroid were plotted and the relative potencies were determined from the IC_{50} values. Comparisons were made of variations in ratios of IC_{50} for each corticosteroids tested. These values were compared with those in the literature and reflected the relative intrinsic potencies of steroids.

Table 2 **A summary of the concentration-response curves for inhibition of TPA-induced epidermal hyperplasia by various steroids showing the values of E_{max}, IC_{50} and gamma (γ) with respect to the Hill equation.**

Corticosteroids	E_{max} (% inhibition)	IC_{50} ($M \times 10^{-4}$)	Gamma (γ)
Alclometasone dipropionate	96.59 ± 7.90 (76.28-116.90)	0.89 ± 0.30 (0.16-1.67)	0.67 ± 0.12 (0.36-0.97)
Betamethasone	94.19 ± 7.33 (75.35-113.04)	13.81 ± 3.73 (4.22-23.39)	0.81 ± 0.11 (0.51-1.10)
Betamethasone dipropionate	95.59 ± 6.55 (82.14-109.04)	0.81 ± 0.36 (0.49-1.13)	0.54 ± 0.06 (0.37-0.71)
Betamethasone valerate	82.24 ± 2.84 (75.69-88.78)	0.15 ± 0.02 (0.10-0.20)	0.94 ± 0.12 (0.66-1.21)
Dexamethasone	90.70 ± 5.72 (76.72-104.69)	1.26 ± 0.44 (0.85-1.67)	0.50 ± 0.08 (0.31-0.69)
Fluocinolone acetonide	89.60 ± 6.93 (70.36 ± 108.85)	0.39 ± 0.14 (0.043-0.78)	0.75 ± 0.23 (0.12-1.38)
Fluocortolone 21-pivalate	85.18 ± 9.51 (58.79-111.58)	0.40 ± 0.15 (0.12-0.68)	0.97 ± 0.30 (0.13-1.82)
Halcinonide	92.55 ± 2.98 (85.25-99.85)	0.97 ± 0.13 (0.66-1.27)	0.78 ± 0.06 (0.62-0.94)
Hydrocortisone	99.04 ± 9.54 (72.56-125.51)	46.18 ± 13.22 (9.47-82.90)	0.96 ± 0.17 (0.49-1.44)
Hydrocortisone acetate	79.63 ± 7.62 (60.04-99.23)	36.67 ± 12.01 (5.80-67.56)	0.79 ± 0.13 (0.46-1.13)
Mometasone furoate	83.31 ± 3.04 (76.11-90.51)	0.23 ± 0.04 (0.14-0.33)	0.79 ± 0.11 (0.53-1.04)
Triamcinolone acetonide	89.80 ± 6.40 (74.14-105.46)	1.13 ± 0.35 (0.28-1.98)	0.75 ± 0.15 (0.39-1.11)

Results are presented as means ± SD. Figures in brackets are confidence intervals

Table 3 **A summary of the concentration-response curves for inhibition of TPA-induced inflammatory cell infiltration by various steroids showing the values of E_{max}, IC_{50} and gamma (γ) with respect to the Hill equation.**

Corticosteroids	E_{max} (% inhibition)	IC_{50} ($M \times 10^{-9}$)	Gamma (γ)
Alclometasone dipropionate	82.12 ± 5.65 (67.58-96.66)	0.32 ± 0.09 (0.10-0.54)	0.97 ± 0.26 (0.31-1.63)
Betamethasone	74.55 ± 3.29 (66.09-83.01)	13.12 ± 1.65 (8.87 ± 17.37)	1.28 ± 0.17 (0.85-1.71)
Betamethasone dipropionate	90.77 ± 3.71 (83.18-98.37)	0.29 ± 0.06 (0.16-0.41)	0.52 ± 0.06 (0.39-0.65)
Betamethasone valerate	73.52 ± 1.76 (69.46-77.57)	0.29 ± 0.03 (0.22-0.34))	0.93 ± 0.07 (0.77-1.09)
Dexamethasone	99.05 ± 10.98 (72.18-125.93)	4.44 ± 1.02 (3.19-5.69)	0.73 ± 0.19 (0.25-1.20)
Fluocinolone acetonide	79.60 ± 2.41 (74.05-85.15)	0.16 ± 0.02 (0.11-0.21)	1.05 ± 0.14 (0.72-1.38)
Fluocortolone 21-pivalate	97.91 ± 12.16 (64.15 ± 131.67)	1.10 ± 0.40 (0.55-1.65)	0.94 ± 0.21 (0.36-1.54)
Halcinonide	90.34 ± 6.29 (74.94-105.74)	0.31 ± 0.05 (0.14-0.48)	0.60 ± 0.11 (0.32-0.88)
Hydrocortisone	100.29 ± 9.36 (71.35-129.23)	61.48 ± 9.66 (39.13-83.83)	0.57 ± 0.26 (0.25-0.89)
Hydrocortisone acetate	79.36 ± 11.49 (59.39-99.33)	77.33 ± 13.85 (60.28-94.58)	1.11 ± 0.27 (0.42-1.80)
Mometasone furoate	89.98 ± 4.88 (78.45-101.51)	0.20 ± 0.05 (0.08-0.33)	0.69 ± 0.14 (0.37-1.01)
Triamcinolone acetonide	77.24 ± 1.26 (74.15-80.33)	0.39 ± 0.03 (0.33-0.46)	1.42 ± 0.11 (1.14-1.70)

5 Results are presented as means ± SD. Figures in brackets are confidence intervals

Tables 2 and 3 provide an estimate of the efficacies (E_{max}), potencies (IC_{50}) and slope of the concentration-response curve (γ) for the 12 corticosteroids investigated in this study. These values were obtained from the Hill equation which is a modified form of the Michaelis-Menton equation.

The apparent excellent correlations between IC_{50} values could indicate that inhibition of inflammation and epidermal hyperplasia are mediated by the same mechanism or else that the limiting factor in producing the two effects was the ability of the steroid to penetrate the skin. The fact that the maximum effects (E_{max}) and slopes (γ) of the concentration-response curves for the two effects were very poorly correlated suggests that different mechanisms are involved in suppressing inflammation and epidermal hyperplasia by the steroids. In addition, the correlations between IC_{50} values are not so impressive when the effects of certain outlier drugs are removed. The effect of removing outliers is shown in Table 4:

Table 4: IC_{50} values (inflammation vs epidermal hyperplasia)

Plot of IC_{50} values (inflammation vs epidermal hyperplasia)	**r** (derived from Hill equation)	**r** (read from graph where IC_{50} = concentration that inhibits half the effect of TPA)
All drugs included	0.961 ($p<0.0005$)	0.909 ($p<0.0005$)
Hydrocortisone and hydrocortisone acetate not included	0.959 ($p<0.0005$)	o.988 ($p<0.0005$)
Hydrocortisone, hydrocortisone acetate, betamethasone dipropionate, dexamethasone and fluocortolone 21-pivalate not included	0.741 ($p = 0.057$)	0.637 ($p = 0.072$)

From the above results it seems likely that the steroids inhibit the inflammatory and hyperplastic effects of TPA by different mechanisms, either inducing different biochemical responses or producing the same response in different cell lines. This conclusion is very relevant to the possible synergistic effects of auranofin are described.

The determination of E_{max} values from the Hill equation could be subject to error due to some uncertainty about measurements made at the top of the concentration-

response curves. Therefore, IC_{50} values were determined by two methods: (a) using the E_{max} value generated from the Hill equation (Tables 5 and 6), and (b) directly from the concentration-response curve, taking the IC_{50} value as that concentration that inhibited 50% of the TPA-induced hyperplasia and inflammation (Tables 7 and 8). The difference between IC_{50} values, and hence relative potencies, determined by the two methods was not great. However, direct reading from the concentration-response curve was considered more reliable and these readings were used for calculating the "synergistic factors" given in Tables 9 and 10.

Table 5 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced epidermal hyperplasia [values generated from the Hill equation where IC_{50} is the concentration that produced 50% of the maximum inhibitory effect (E_{max})].**

Corticosteroids	IC_{50} for inhibition of epidermal thickening ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	36.67	1.0
Hydrocortisone	46.18	0.79
Betamethasone	27.25	1.35
Dexamethasone	1.26	29.10
Triamcinolone acetonide	1.13	32.45
Halcinonide	0.97	37.80
Alclometasone dipropionate	0.89	41.20
Betamethasone dipropionate	0.81	45.27
Fluocortolone 21-pivalate	0.4	91.68
Fluocinolone acetonide	0.39	94.03
Mometasone furoate	0.23	159.43
Betamethasone valerate	0.15	244.47

Table 6 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced inflammatory cell infiltration into the dermis [values generated from the Hill equation where IC_{50} is the concentration that produced 50% of the maximum inhibitory effect (E_{max})].**

Corticosteroids	IC_{50} for inhibition of inflammatory cell infiltration in the dermis ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	77.33	1.0
Hydrocortisone	61.48	1.26
Betamethasone	13.12	5.89
Dexamethasone	4.44	17.42
Fluocortolone 21-pivalate	1.10	70.30
Triamcinolone acetonide	0.39	198.28
Alclometasone dipropionate	0.32	241.66
Halcinonide	0.31	249.45
Betamethasone dipropionate	0.29	266.66
Betamethasone valerate	0.29	266.66
Mometasone furoate	0.20	386.65
Fluocinolone acetonide	0.16	483.31

Table 7 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced epidermal hyperplasia (values taken from concentration-response curve where IC_{50} is the concentration that inhibited 50% of the TPA effect).**

Corticosteroids	IC_{50} for inhibition of epidermal thickening ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	70.00	1.0
Hydrocortisone	45.10	1.55
Betamethasone	50.00	1.40
Dexamethasone	2.00	35.0
Triamcinolone acetonide	1.40	50.0
Betamethasone dipropionate	1.40	50.0
Halcinonide	1.10	63.64
Alclometasone dipropionate	1.00	70.0
Fluocortolone 21-pivalate	0.60	116.67
Mometasone furoate	0.40	175.0
Betamethasone valerate	0.22	318.18
Fluocinolone acetonide	0.21	333.33

Table 8 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced inflammatory cell infiltration into the dermis (values taken from concentration-response curve where IC_{50} is the concentration that inhibited 50% of the TPA effect).**

Corticosteroids	IC_{50} for inhibition of inflammatory cell infiltration in the dermis ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	110.0	1.0
Hydrocortisone	60.0	1.83
Betamethasone	21.0	5.23
Dexamethasone	4.10	26.83
Fluocortolone 21-pivalate	1.10	100.0
Triamcinolone acetonide	0.70	157.14
Betamethasone valerate	0.65	169.23
Alclometasone dipropionate	0.60	183.33
Halcinonide	0.60	183.33
Betamethasone dipropionate	0.40	275.0
Mometasone furoate	0.30	366.67
Fluocinolone acetonide	0.25	440.0

In the present study, hydrocortisone, hydrocortisone acetate, betamethasone and dexamethasone had low to medium potencies with respect to both inhibition of TPA-induced epidermal hyperplasia and TPA-induced inflammatory cell infiltration. This ranking was consistent with corresponding potencies in clinical setting that was shown in Table 1.

Halcinonide, triamcinolone acetonide, alclometasone dipropionate, betamethasone dipropionate, fluocortolone 21-pivalate were found to have medium to strong potencies in inhibition of TPA-induced epidermal hyperplasia and inflammatory cell infiltration, and these values were consistent with the clinical potencies.

Finally, mometasone furoate, betamethasone valerate, betamethasone dipropionate, and fluocinolone acetonide had strong to very strong potencies for TPA-induced epidermal hyperplasia. Amongst them, betamethasone valerate was shown to be the most potent agent. When their potencies for inhibition of TPA-induced inflammatory cell infiltration were investigated, they were also shown to have strong to very strong anti-inflammatory effect. Fluocinolone acetonide was found to be the most potent agent, with a relative potency of 483 (Table 6) or 440 (Table 8).

When comparisons were made between the relative potencies of the steroids tested in this study and their respective clinical potencies, the order of potency was generally the same.

It might be expected that a particular corticosteroid would have equal potency with respect to anti-hyperplastic and anti-inflammatory actions. Our results showed that these reactions were not necessarily closely related. Linear regression of the relative potencies for inhibition of the hyperplastic effects of the steroids vs relative potencies for suppression of inflammation gave a value $r = 0.573$ ($p = 0.51$) for data from tables 5 and 6 and a value of $r = 0.658$ ($p<0.02$) for values in tables 7 and 8. Thus, about 65% of the variance between the two actions seems to be due to some common property (which could be lipid solubility) but a significant component of these actions differs with respect to suppression of hyperplasia and suppression of inflammation. This is also illustrated by comparing the rank orders of potency in Tables 7 and 8. Only six of the 12 steroids have the same rank for both effects and, of these steroids, four are the four least potent.

Example 2: Synergistic Effect Of Auranofin And Corticosteroids With Different Clinical Potencies

Results of preliminary studies indicated that auranofin, under certain conditions, can inhibit some of the effects of TPA, although it is not particularly potent in this regard.

The present study examines whether combinations of auranofin and corticosteroids had a synergistic effect in suppressing TPA lesions.

Four corticosteroids with different clinical potencies ranging from weak to strong were chosen, namely, hydrocortisone, fluocinolone acetonide, betamethasone dipropionate and mometasone furoate. TPA was premixed with the corticosteroids in the presence or absence of a fixed concentration of auranofin (0.2%) to produce the required concentrations and applied to the backs of mice immediately. Concentration-response curves were determined by non-linear regression using least squares fitting. IC_{50} values were determined by reading the value from the graph that corresponded to 50% of the effect produced by TPA (Tables 9 and 10).

The term 'apparent IC_{50}' refers to the value for the combination of steroid and auranofin.

Table 9 **Apparent IC_{50} values obtained from the computer fitted graph for the effects on TPA-induced epidermal hyperplasia of four corticosteroids in the absence and presence of auranofin (0.2%).**

Corticosteroids	Apparent IC_{50} ($M \times 10^{-4}$)		
	without auranofin	with auranofin	Synergistic factor
Betamethasone dipropionate	1.40 ± 0.36	0.025 ± 0.003	56.0
Hydrocortisone	45.00 ± 13.22	22.00 ± 11.23	2.05
Fluocinolone acetonide	0.21 ± 0.14	0.016 ± 0.002	13.13
Mometasone furoate	0.40 ± 0.04	0.31 ± 0.05	1.29

Results are presented as means ± SD.

Table 10 **Apparent IC_{50} values obtained from the computer fitted graph for the effects on TPA-induced dermal inflammatory cell infiltration of four corticosteroids in the absence and presence of auranofin (0.2%).**

Corticosteroids	Apparent IC_{50} ($M \times 10^{-4}$)		
	without auranofin	with auranofin	Synergistic factor
Betamethasone dipropionate	0.40 ± 0.06	0.090 ± 0.016	4.44
Hydrocortisone	60.00 ± 9.66	31.00 ± 4.12	1.94
Fluocinolone acetonide	0.25 ± 0.002	0.11 ± 0.013	2.27
Mometasone furoate	0.30 ± 0.05	0.008 ± 0.001	37.50

Results are presented as means ± SD.

The value termed the 'synergistic factor' is defined as the IC_{50} value for the steroid determined in the absence of auranofin divided by the IC_{50} for the same steroid determined in the presence of auranofin (0.2%).

Synergism refers to situations in which a combination of two drugs produces an effect that is significantly greater than the algebraic sum of the effects when the same dose or concentration of each drug is observed separately in the same test system. Synergism can result in a multifold potentiation of the effects of one or both drugs or it can give rise to effects that are qualitatively different from those elicited by the drugs when used separately.

With respect to effects on epidermal hyperplasia, only two of the four steroids tested could be regarded as showing a synergistic reaction with auranofin, namely betamethasone dipropionate and fluocinolone acetonide. From results depicted in Tables 9 and 10 it can be seen that in the case of betamethasone dipropionate and fluocinolone acetonide, the per cent increase in the apparent potencies of the steroids is 5,600% and 1,300%, respectively. However, in the case of the least potent of the four steroids, namely, hydrocortisone, the apparent increase in potency was 100%. A more effective

way of demonstrating the presence of true synergism is to compare separately the following:

1) auranofin (0.2%) alone,
2) a low concentration of steroid alone (sufficient to inhibit about 20% of the effects of TPA — this value can be read from the concentration-response curve for the steroid when studied alone),
3) the same concentration of steroid as in (2) combined with auranofin (0.2%) — this value can be obtained from the dose-response curve for steroid in the presence of auranofin, and
4) a concentration of the same steroid used in (2) but in sufficient concentration as to produce the same effect as that achieved in (3).

If the effects of (3) appear to be the summation of (1) and (2), the result is not synergism. If the effects of (3) greatly exceed those of (1) and (2) if added arithmetically, the result is synergism according to our definition.

The results for epidermal hyperplasia are displayed in Figure 1. Auranofin alone inhibited TPA-induced epidermal hyperplasia by about 10% in all four studies. Betamethasone dipropionate 1×10^{-5} M alone caused about 20% inhibition of TPA effect. The combination of betamethasone dipropionate (1×10^{-5} M) and auranofin (0.2%) produced about 65% inhibition of TPA effect. To gauge the significance of the increased effect that resulted when auranofin was added to betamethasone dipropionate, comparison should be made with the concentration of betamethasone dipropionate that, in the absence of auranofin, produced the same effect. This value was 5×10^{-4} M or 50 times the concentration that produced the same effect in the presence of auranofin.

With respect to epidermal hyperplasia, the studies demonstrate that: (a) a massive synergism results when auranofin is added to betamethasone dipropionate and to fluocinolone acetonide; (b) a minor degree of synergism may result from the combination of hydrocortisone and auranofin; and (c) that no synergism or even additive effect results when auranofin is co-administered with mometasone furoate.

With respect to inflammatory cell infiltration into the dermis, the results in Table 10 indicate that the effects of a combination of auranofin (0.2%) and mometasone furoate is the result of synergism since the apparent IC_{50} is increased by about 3,800%. It is also possible that a lesser degree of synergism occurs with respect to the anti-

inflammatory action of betamethasone dipropionate in the presence of 0.2% auranofin. Here the increase in apparent IC_{50} is of the order of 400-500% (Table 10).

The results in Figure 2 show a massive synergism between mometasone furoate (5×10^{-6} M) and auranofin (0.2%). This combination produced an effect that was equal to that produced by 1×10^{-3} M mometasone in the absence of auranofin. Figure 2 also indicates that synergism may exist for the combination of auranofin with betamethasone dipropionate and fluocinolone acetonide, but not with hydrocortisone.

The results of these studies indicate that extensive synergism results from the combination of auranofin with certain corticosteroids, such as for example betamethasone dipropionate and fluocinolone acetonide as regards reduction of epidermal hyperplasia, and with others such as for example mometasone furoate as regards reduction of inflammation. Lesser degrees of synergism may exist between auranofin and other steroids.

Gold compounds and corticosteroids, as well as their formulations, which can be suitably used in the present invention have been discussed in detail in the present application or in Australian patent No. 616 755, which is incorporated herein by reference.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

2 A method of treating an immune-mediated disorder according to claim 1 wherein the disorder has an inflammatory component and a cellular hyperproliferation component.

3. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid are administered simultaneously.

4. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid are administered sequentially.

5. A method of treating an immune-mediated disorder according to claim 4 wherein the at least one corticosteroid is administered after the gold compound.

6. A method of treating an immune mediated disorder according to any one of the preceding claims comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

7. A method according to any one of the preceding claims, wherein the disorder is an immune-mediated dermatological disorder.

8. A method according to claim 7, wherein the disorder is psoriasis.

9. A method according to claim 7, wherein the disorder is dermatitis.

10. A method according to any one of claims 1 to 6 wherein the disorder is rheumatoid arthritis.

11. A method according to any one of the preceding claims, wherein the gold compound is lipid soluble.

12. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards cellular hyperproliferation in preference to inflammation.

13. A method according to claim 12, wherein the at least one corticosteroid is selected from the group consistin of betamethasone dipropionate, fluocinolone acetonide and hydrocortisone.

14. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards inflammation in preference to cellular hyperproliferation.

15. A method according to claim 14, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and mometasone furoate.

16. A method according to claim 10 wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

17. A method according to claim 16 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

18. A method according to any one of the preceding claims wherein the gold compound is auranofin.

19. A method according to any one the preceding claims, wherein the gold compound is administered systemically.

20. A method according to any one of claims 1 to 18, wherein the gold compound is administered orally.

21. A method according to any one of claims 1 to 18, wherein the gold compound is administered locally.

22. A method according to any one of claims 1 to 18, wherein the gold compound is administered topically.

23. A method according to any one of claims 1 to 18, wherein the gold compound is administered by intra-articular injection.

24. A method according to any one of the preceding claims, wherein the at least one corticosteroid is administered systemically.

25. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered orally.

26. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered locally.

27. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered topically.

28. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered by intra-articular injection.

29. A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

30. A pharmaceutical composition according to claim 29, wherein the composition is formulated for systemic administration.

31. A pharmaceutical composition according to claim 29, wherein the composition is formulated for oral administration.

32. A pharmaceutical composition according to claim 29, wherein the composition is formulated for local administration.

33. A pharmaceutical composition according to claim 29, wherein the composition is formulated for topical administration.

34. A pharmaceutical composition according to claim 29, wherein the composition is formulated for administration by intra-articular injection.

35. A pharmaceutical composition according to any one of claims 29 to 34, wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

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36. A method according to claim 35 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. A method according to any one of claims 29 to 36, wherein the gold compound is auranofin.

DATED this 22nd Day of September 1998

MEDICAL INNOVATIONS LIMITED

Attorney: PAUL G. HARRISON
Fellow Institute of Patent Attorneys of Australia
of BALDWIN SHELSTON WATERS

ABSTRACT

This invention relates to a method of treating an immune-mediated disorder having one or more manifestations. The method comprises administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact synergistically with the gold compound to exhibit preferential action towards one of the manifestations of said disorder or to exhibit equal action towards each manifestation of said disorder. The invention also relates to a pharmaceutical composition suitable for use in the method.

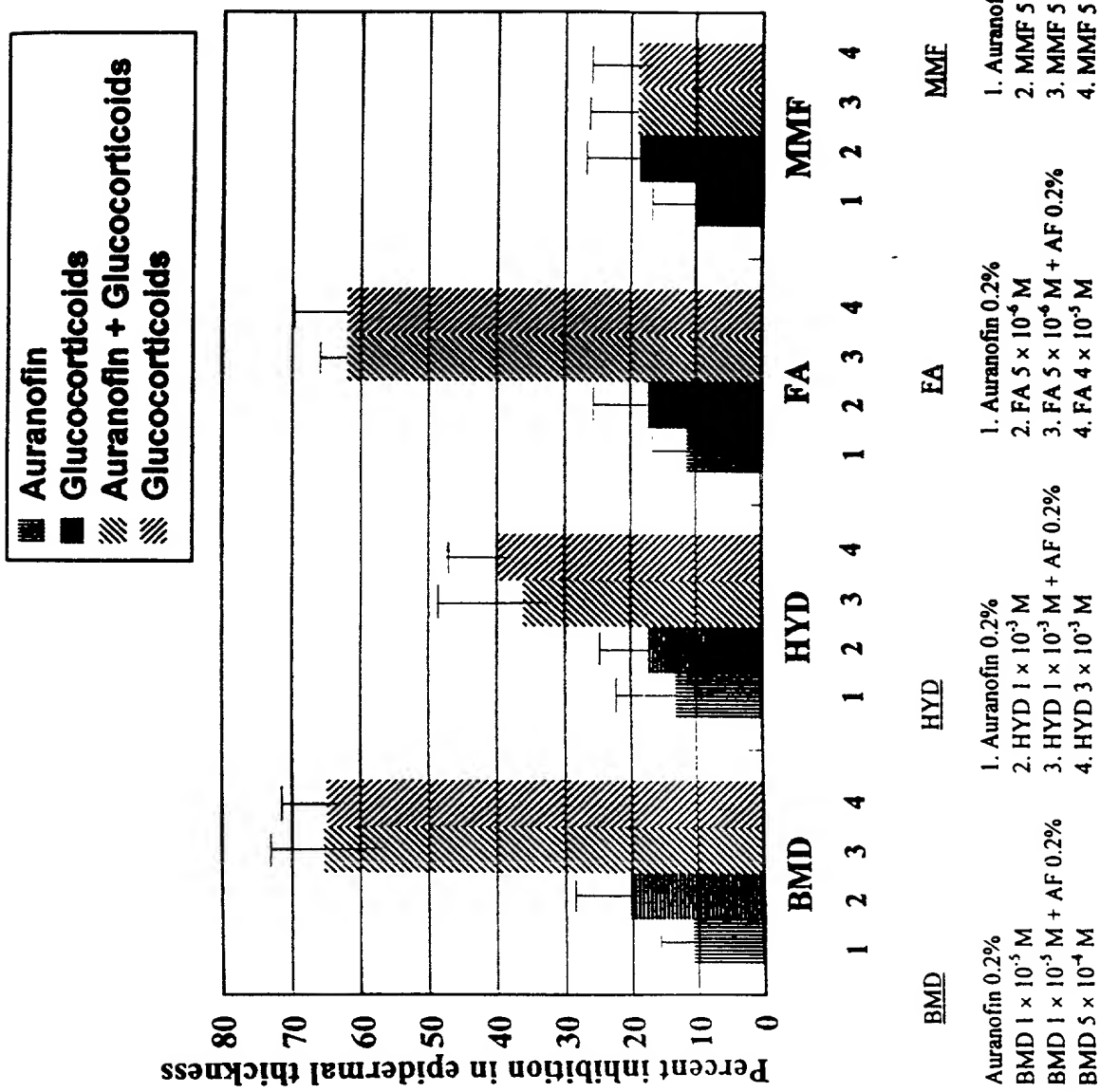
Auranofin
Glucocorticoids
Auranofin + Glucocorticoids
Glucocorticoids
Percent inhibition in epidermal thickness
0
10
20
30
40
50
60
70
80
1 2 3 4 BMD 1 2 3 4 HYD 1 2 3 4 FA 1 2 3 4 MMF
BMD
1. Auranofin 0.2%
2. BMD 1 × 10⁻⁵ M
3. BMD 1 × 10⁻³ M + AF 0.2%
4. BMD 5 × 10⁻⁴ M
HYD
1. Auranofin 0.2%
2. HYD 1 × 10⁻³ M
3. HYD 1 × 10⁻³ M + AF 0.2%
4. HYD 3 × 10⁻³ M
FA
1. Auranofin 0.2%
2. FA 5 × 10⁻⁶ M
3. FA 5 × 10⁻⁶ M + AF 0.2%
4. FA 4 × 10⁻³ M
MMF
1. Auranofin 0.2%
2. MMF 5 × 10⁻⁶ M
3. MMF 5 × 10⁻⁶ M + AF 0.2%
4. MMF 5 × 10⁻⁶ M

FIGURE 1

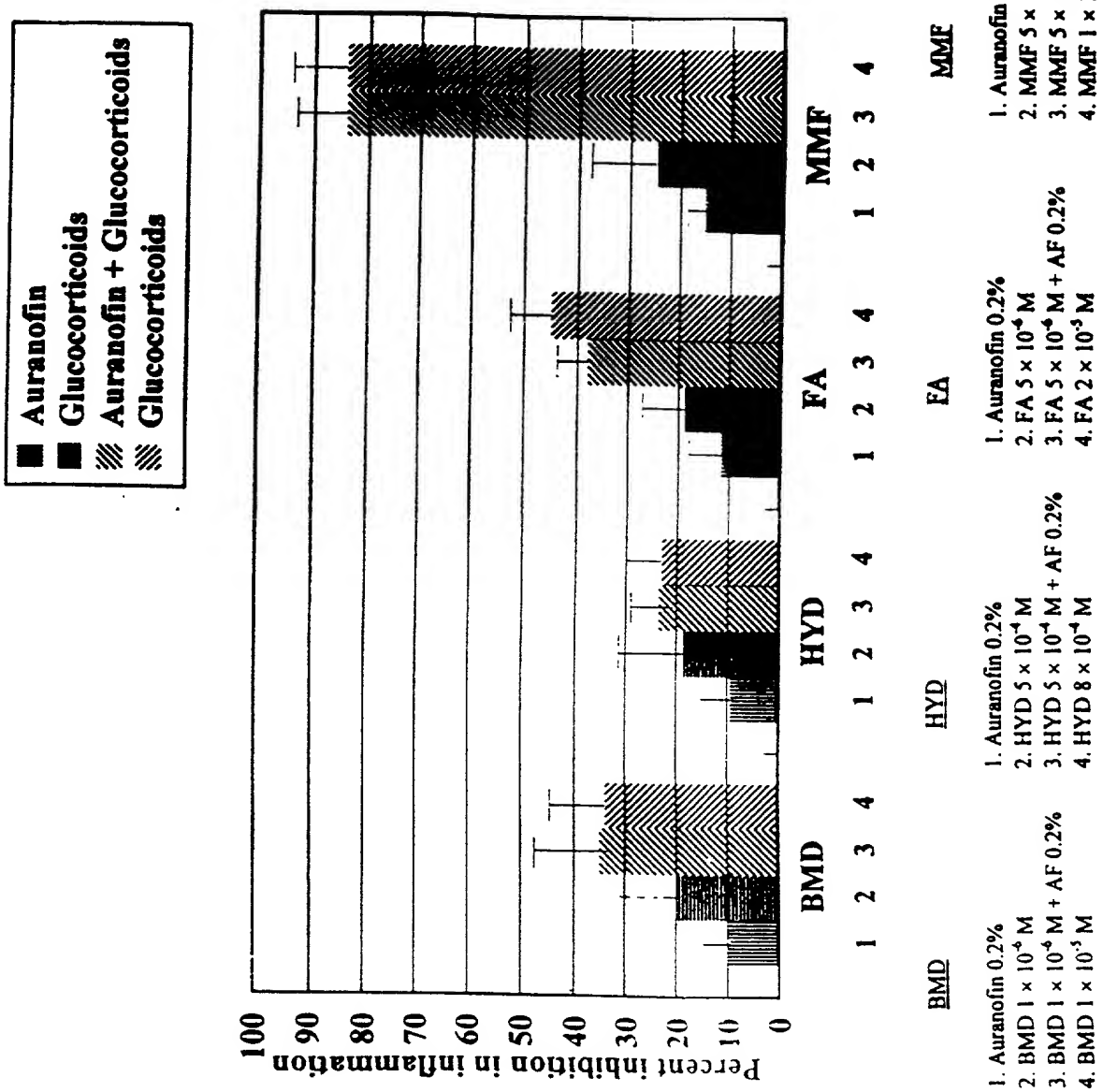
Auranofin
Glucocorticoids
Auranofin + Glucocorticoids
Glucocorticoids
Percent inhibition in inflammation
0
10
20
30
40
50
60
70
80
90
100
1 2 3 4
BMD
1 2 3 4
HYD
1 2 3 4
FA
1 2 3 4
MMF
BMD
1. Auranofin 0.2%
2. BMD 1 × 10⁻⁶ M
3. BMD 1 × 10⁻⁶ M + AF 0.2%
4. BMD 1 × 10⁻³ M
HYD
1. Auranofin 0.2%
2. HYD 5 × 10⁻⁴ M
3. HYD 5 × 10⁻⁴ M + AF 0.2%
4. HYD 8 × 10⁻⁴ M
FA
1. Auranofin 0.2%
2. FA 5 × 10⁻⁴ M
3. FA 5 × 10⁻⁴ M + AF 0.2%
4. FA 2 × 10⁻³ M
MMF
1. Auranofin 0.2%
2. MMF 5 × 10⁻⁴ M
3. MMF 5 × 10⁻⁴ M + AF 0.2%
4. MMF 1 × 10⁻³ M

FIGURE 2

DECLARATION, PETITION AND POWER OF ATTORNEY FOR PATENT APPLICATION

(Check one):

- ☐ Declaration Submitted with Initial Filing
- ☒ Declaration Submitted after Initial Filing

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entit'ed:

SYNERGISTIC GOLD-CONTAINING COMPOSITIONS

the specification of which (check one):

☐ is attached hereto.

OR

☒ was filed on **04 November 1997** as PCT International Application Number **PCT/AU97/00747**

☐ and was amended by PCT Article 19 Amendment on _____ (if applicable),

☒ and was amended by PCT Article 34 Amendment on **22 September 1998** (if applicable).

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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Giulio A. DeConti, Jr.	Reg. No. 31,503	Faustino A. Lichauco	Reg. No. 41,942
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Jane E. Remillard, (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor **Richard Edward THOMAS**
Inventor's signature R Thomas Date 30/5/1999
Residence **14 Parnell Street, Killara, NSW 2071, Australia** AUX
Citizenship **Australia**
Post Office Address (if different) **same as above**

PRIORITY CLAIM

(Check one):

☐ no such applications have been filed.

☒ such applications have been filed as follows

1) **FOREIGN PRIORITY CLAIM:** I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (dd/mm/yyyy)	Priority Not Claimed	Certified Copy Attached	
				Yes	No
PO 3473	**AU**	**04 Nov 1996 (04.11.96)**	☐	☐	☒
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

2) **PROVISIONAL PRIORITY CLAIM:** I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Provisional Application Number(s)	Filing Date (dd/mm/yyyy)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

3) **U.S./PCT PRIORITY CLAIM:** I hereby claim the benefit under Title 35, United States Code, §120 of any United States application or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (dd/mm/yyyy)	Parent Patent Number *(if applicable)*
	PCT/AU97/00747	**04 November 1997 (04.11.97)**	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.